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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/101,413	08/07/98	STAUSS	H RPMS102

EXAMINER	
LUBET, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/101,413	Stauss
Examiner	**Group Art Unit**
Lubet	1644

☒ Responsive to communication(s) filed on *Oct. 29, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18, 20-43, and 45-49* is/are pending in the application.

Of the above, claim(s) *10-13, 20-43, and 45-49* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9 and 14-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 第7

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This office action is in response to Paper 9 filed Oct. 29, 1999.

2. Claims 1-18, 20-43 and 45-49 are pending.

3. Examiner acknowledges the election with traverse of Group II, claims 1-18 in the above mentioned Paper 9. Applicant has traversed the restriction under PCT Rule 13.1. Applicant urges that the special technical feature of the claims is an allorestricted CTL and that Melief et al. does not teach allorestricted CTL. However Yin et al. (Eur. J. Immunology 24:1988, 1994) teach a clonal population of cytotoxic T lymphocytes reactive against a selected molecule expressed in target cell having a different HLA class I equivalent (H-2) from the CTL cells (see abstract and Figure 1, in particular). Therefore the **lack of unity is maintained**. Applicant have further elected a species of method of treating a patient with a disease by administering CTL specific for cells expressing GATA-1 and WT-1 and the disease is a hematological malignancy. Claims 10-13 are not directed to hematological diseases expressing GATA-1 and WT-1 and are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 20-43 and 45-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-9 and 14-18 are under examination and are examined as they read upon a method of treating hematological disease expressing GATA-1 and WT-1 by administering CTL specific for cells expressing GATA-1 and WT-1.

4. **SEQUENCE RULES**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The sequence on page 44, line 1 requires a Seq ID NO. but a CRF and paper copy of CRF has not been submitted. Applicant should review the specification to determine is any additional sequences requiring SEQ ID NO:s are disclosed in the specification.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. In the oath, applicant claims foreign priority under 119(a-d) based on PCT/GB97/00118. However, since this application is filed under 35 USC 371, Applicant should not claim priority to PCT/GB97/00118 under 119(a-d) in the oath. **A new oath is required.**

7. **Drawings**

The disclosure is objected to because of the following informalities: The specification on pages 39-41 discloses descriptions of the drawings. The specification should be amended to identify this section of the specification as "BRIEF DESCRIPTION OF THE FIGURES". Applicant is requested to amend the description of the drawings for Figures 3-6 to specify the different parts (IE Figure 3 A-D) of each figure . See MPEP 608.01(f) and (g).

8. Claims 1-9 and 14-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Reasons are set forth below.

A. Claim 5 contains a typographical error. "Mutuant" should be "mutant".

B. In claim 1 it is unclear what the term "diseased cells which cells contain or are associated with an abnormal molecule or abnormally elevated amount of a molecule" means. It is unclear what the term "cells are associated with means". Does the term mean that the cells express an abnormal molecule or increased amount of a molecule?

It is unclear what the term "abnormal molecule" means. Is this term limited to a molecule containing a mutation? Does the term encompass molecules that are expressed in a transformed or virus infected cell but are not expressed in a "normal cell" (IE untransformed or uninfected" cell)? Does the term encompass cells which are transformed with a nucleic acid encoding a molecule IE tumor antigen, viral antigen, cellular protein such as HLA molecule derived from another allotype or species?

C. In claim 1, lines 4 and 9, it is unclear what the term "HLA class I or equivalent" molecule" means. It is unclear what molecules are equivalent to HLA class I molecules. Must the "HLA equivalent" comprise an antigen binding cleft? In the absence of clarification the term is

examined broadly to encompass any class I molecule, including murine MHC Class I molecule (IE H-2 K molecule).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 1-9, 14, 16 and 18 are rejected under 35 USC 102(e) as anticipated by Slavin et al. 5,928,639 (priority to March 17, 1994) as evidenced by Wu et al. (J. Biological Chemistry 270:5944, 1995).

Slavin et al. teach a method for treating leukemia by administering allogenic CTL from an individual which does not carry the HLA class I molecule or equivalent of the patient.

Slavin et al. teach a murine model of B cell leukemia (BCL1) in which BALB/C (H-2 d) mice develop leukemia when inoculated with syngeneic B cell leukemic cells . Slavin et al. also teach that method of treating leukemia in this model by administering allogenic C57 (H-2 b) spleen and lymph node cells and Il-2 to BALB/c (H-2d) mice (see column 13, lines 40-59, in particular).

Slavin also teach treatment of human leukemia patients by administering allogenic PBL (which contain a plurality CTL clones) in which allogenic PBL are obtained from a donor which is HLA mismatched (see column 18,, lines 36-55 and column 19, lines 1-19, claims 1-2 and 14 , in particular).

Wu et al. teach that leukemic cells express GATA1 and WT1, therefore the methods of treating leukemia taught by Slavin et al. read upon the elected species of the invention claimed in claims 1-9 and 14-18.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-9 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohler et al. (Cancer Immunol. Immunother 2674, 1988) or Kawakami et al. US 5,994,523 (priority to April 22, 1994) in view of Yin et al. (Eur. J. Immunol. 24:1988, 1994) or Huang et al. (Cancer Immunol. Immunother 38:399, 1994), Slavin et al . 5,928,639 (priority to March 17, 1994) or Wu et al. (J. Biol. Chem 270:5944, 1995).

Kohler et al. teach a method of treating a cancer patient by administering allogenic T lymphocytes which have been activated in vivo or in vitro (see page 74, right column, in particular). Kohler et al. also teach that the use of allogenic lymphocytes is an alternative to autologous cells obtained from patients who are immuncomprimised from their disease as well as previous treatment. Kohler et al. teach that the antitumor capabilities of allogeneic immune cells is suggested clinically by the graft-versus-leukemia (GVL) effect seen in allogenic bone marrow transplantation for leukemia and that, in murine models, prior alloactivation of cells from the allogenic donor strain results in expansion of an effector population with enhanced antitumor activity and no apparent augmentation in GVHR. Kohler et al. teach that the antitumor effect is immune mediated .

Kawakami et al. disclose methods of treating cancer patients by administering CTL specific for cancer cells which express an abnormal molecule (IE MART-1) wherein the molecule is capable of being presented on the surface of cells by a HLA class I molecule. Kawakami et al. teach a library of melanoma specific CTL prepared by inducing melanoma specific CTL lines by culturing peripheral blood cells (PBL) with a melanoma cell line (see column 30, lin 46 through column 32, line 50, in particular). Kawakami et al. also teach a method treating a patient with metastic melanoma by administering melanoma specific CTL (see column 36, line 60 through column 15, in particular).

Kawakami et al. and Kohler et al. do not teach a method of treating a hematological disease expressing GATA1 and WT1 by administering CTL derived from an individual which does not carry the HLA class. I or equivalent molecule of the patient.

However Yin et al. (Eur. J. Immunology 24:1988, 1994) teach a library of of cytotoxic T lymphocytes (CTL PCT/GB97/0011) clones reactive against a selected molecule ($RAS^{Val\ 12}$) expressed in target cell having a different HLA class I equivalent (H-2) from the CTL cells (see abstract and Figure 1, in particular). Yin et al. further teach that CTL are specific for the $RAS^{Val\ 12}$ used to induce CTL and not allogeneic H-2 molecule and that the CTL are CD8+, α, β TCR + cells. Yin et al. further teach that MHC class I molecules appear to be required since only peptide-treated class I positive but not negative cells are lysed by CTL lines (see Figure 2 and page 1990, in particular). Yin et al. further teach that unrestricted CTL (IE CTL that lyse antigen pulsed cells which have a different MHC Class I molecule) have been demonstrated which are reactive to mucin expressed by breast cancers or peptide fragments of ovalbumin (see page 1992 in particular).

Huang et al. teach human , clonal CD8+ CTL lines capable of lysing melanoma cells with which they have no HLA class I alleles in common. Huang et al. also teach that the lysis was mediated by the HLA class I molecule. Thus Huang et al. teach alloreactive CTL lines that lyse tumor cells having a different HLA MHC Class I molecule than the CTL (see abstract, Table 3, and pages 401-403, in particular). Huang et al. also teach that "recent studies revealed that lysis of human tumor cells by CTL was less restrictive than that by virus specific CTL." Huang et al also teach that a portion of CD8+ T cell line isolated by stimulating with allogeneic (HLA class I mismatched) tumor cells are melanoma -specific. Huang et al. term CTL which have the ability to recognize and lyse cells presenting antigen with which they had no HLA class I allele in common as " non-fastidious CTL". Huang et al. also teach that "non-fastidious recognition" may be an integral part of most or all antigen specific T cell response . Hunag et al. also teach that the human T cell response to melanoma appears to be directed at antigens that are identical or nearly identical to normal self proteins and that the repertoire of CTL to tumor antigens may be more limited than those directed to foreign antigens. Huang et al. teach that non-fastidious CTL

were significantly represented among CTL clones derived from both autologous and allogeneic MLTC. Huang et al. also teach that allogenic melanomas may substitute for autologous tumors in adoptive T cell immunotherapy and that allogeneic stimulation may induce a wider spectrum of tumor reactive T cells (see page 404, in particular).

Slavin et al. has been discussed supra. As summarized supra, Slavin et al. teach administration of allogeneic cells to treat leukemia.

Wu et al. teach that leukemia is a hematological disease in which the leukemic cells express GATA1 and WT1 (see page 5944, in particular).

Therefore one with ordinary skill in the art at the time of the invention would be motivated to make CTL specific for leukemia cells using the techniques taught by the prior art and to select CTL which are specific for leukemia cells but are capable of lysing allogeneic (HLA mismatched) leukemia cells using the methods taught by Yin et al. or Huang et al. to isolate such CTL and to administer such cells to patients using the methods used taught by Kawakami et al. One with ordinary skill in the art at the time of the invention would be motivated to administer such CTL to leukemic patients that do not have same HLA haplotype as the CTL since Huang et al. teach that allostimulation to tumor antigens induces a wider spectrum of tumor reactive T cells specific for tumor cells and with the expectation that the allogenic CTL cells would kill tumor cells and that the tumor cells burden would be reduced. Based upon the teachings of Kohler et al. and Slavin et al. one with ordinary skill in the art would expect that allogenic CTL specific could be administered safely.

The invention claimed in claim 15 differs from the prior art in that the method of determining HLA class of patient is not specifically identified or does not use DNA typing to identify the HLA haplotype. However, the specification on page 10 teaches that DNA typing to identify the HLA haplotype of an individual is well known in the art. Therefore it would be obvious to one with ordinary skill in the art to use admitted prior art methods of DNA typing to identify the HLA haplotype of the patient prior to administering CTL and to select CTL which are HLA mismatched for the reasons discussed supra.

14. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

15 No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

Jan. 18, 2000

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1600